Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma

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Summary

Background Previous studies on prognostic factors in stage I invasive epithelial ovarian carcinoma have been too small for robust conclusions to be reached. We undertook a retrospective study in a large international database to identify the most important prognostic variables.

Methods 1545 patients with invasive epithelial ovarian cancer (International Federation of Gynaecology and Obstetrics [FIGO] stage I) were included. The records of these patients were examined and data extracted for univariate and multivariate analysis of disease-free survival in relation to various clinical and pathological variables.

Findings The multivariate analyses identified degree of differentiation as the most powerful prognostic indicator of disease-free survival (moderately *vs* well differentiated hazard ratio 3·13 [95% CI 1·68–5·85], poorly *vs* well differentiated 8·89 [4·96–15·9]), followed by rupture before surgery (2·65 [1·53–4·56]), rupture during surgery (1·64 [1·07–2·51]), FIGO 1973 stage Ib *vs* Ia 1·70 [1·01–2·85]) and age (per year 1·02 [1·00–1·03]). When the effects of these factors were accounted for, none of the following were of prognostic value: histological type, dense adhesions, extracapsular growth, ascites, FIGO stage 1988, and size of tumour.

Interpretation Degree of differentiation, the most powerful prognostic indicator in stage I ovarian cancer, should be used in decisions on therapy in clinical practice and in the FIGO classification of stage I ovarian cancer. Rupture should be avoided during primary surgery of malignant ovarian tumours confined to the ovaries.

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Introduction

About 25% of patients with common invasive epithelial ovarian carcinoma are first seen with disease confined to the ovaries (International Federation of Gynaecology and Obstetrics [FIGO] stage I).[1] 5-year survival rates of 70–90% have been reported for invasive stage I ovarian carcinoma.[1–10] Classic clinical and pathological prognostic factors, such as degree of differentiation, FIGO substage, histological type, dense adhesions, large-volume ascites, rupture before surgery, extracapsular growth, and age of the patient, have been identified by multivariate analyses as independent prognostic characteristics,[2–10] and other factors, such as rupture during surgery, bilaterality, and positive peritoneal cytology, were of prognostic significance in some univariate analyses. Degree of differentiation is the only factor with independent prognostic value in all published multivariate analyses.

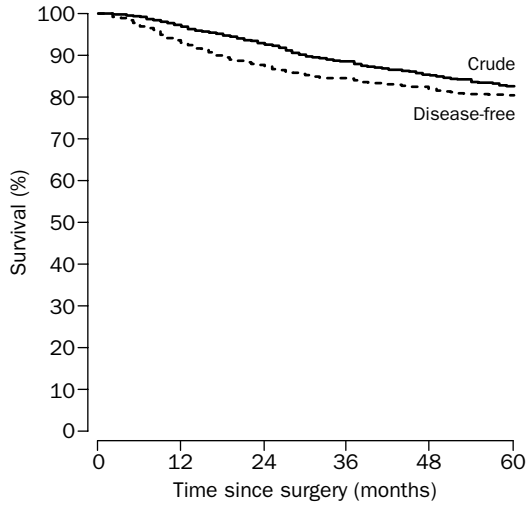
On the other hand, the latest FIGO subclassification of stage I distinguishes patients with unilateral tumours (stage Ia) from those with bilateral tumours (stage Ib) and separately identifies tumour spillage, extracapsular growth, and positive peritoneal cytology (stage Ic).[11] This classification implies that the factors that assign a patient to substage Ib or Ic carry a worse prognosis than those associated with substage Ia. However, this classification does not take into account the degree of differentiation.

The main limitation of the conclusions derived from previous retrospective analyses is that the sample sizes of most were too small for some independent prognostic variables to be detectable with sufficient power. The aim of our study was to identify the significant prognostic clinical and pathological factors in stage I invasive epithelial ovarian carcinoma in a much larger database. In addition, because of the increasing trend to use laparoscopic surgery, in reviewing all patients' records, we paid special attention to the occurrence and timing of tumour rupture and to the presence of dense adhesions.

Methods

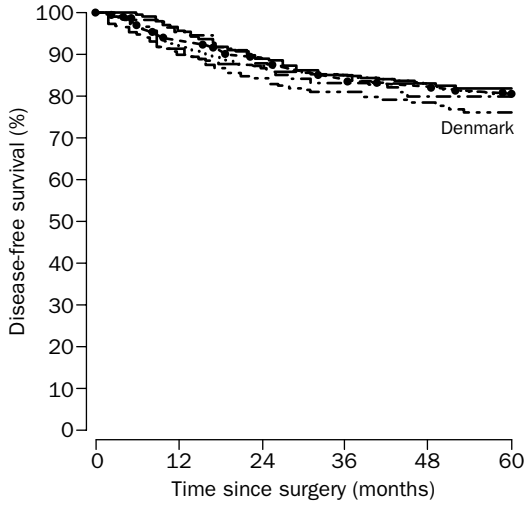
Patients

Patients with invasive epithelial FIGO stage I ovarian cancer were included. The records of six existing databases[2,3,6–9] were retrospectively reanalysed according to predefined criteria. The Norwegian cohort consisted of 380 patients referred to the Norwegian Radium Hospital between Jan 1, 1980, and July 1, 1998. The 277 Danish patients were treated between September, 1981, and September, 1986, and registered in the Danish Ovarian Cancer Study Group (DACOVA) register. Canadian patients (n=242) were treated at the Princess Margaret Hospital, Toronto, between April 1, 1971, and Dec 31, 1982. The patients from the UK



Number at risk						
Crude survival	1545	1405	1286	1141	965	791
Disease-free survival	1545	1339	1204	1075	909	746

Figure 1: **Actuarial disease-free and crude survival**



Number at risk						
Norway	380	343	318	302	233	164
Canada	242	231	211	201	190	183
Sweden	267	237	226	215	208	199
Austria	121	107	92	79	64	50
Denmark	277	245	202	141	103	56
UK	258	175	155	133	108	89

Figure 2: **Actuarial disease-free survival by country**

(n=258) were referred to the Royal Marsden NHS Trust London, between January, 1980, and December, 1994. The 267 Swedish patients were referred to the Radiumhemmet, Stockholm, in the period 1974–86. 121 Austrian patients were treated at the First Department of Obstetrics and Gynecology of the University of Vienna between December, 1975, and June, 1987. Median follow-up was 62 months (range 21–112) in Norway, 43 months (11–104) in Denmark, 111 months (36–91) in Canada, 55 months (0–185); three patients lost to follow-up within a month) in the UK, 121 months (23–216) in Sweden, and 68 months (5–193) in Austria.

Procedures

Follow-up of the original databases was updated whenever possible. Patients from the original databases with ovarian borderline tumours, concurrent or previous malignant disease, or disease of stage II or higher were excluded. Patients with adhesions and microscopic tumour invasion of adjacent structures were classified as stage II or III. After these exclusions, the new dataset consisted of 1545 patients with stage I invasive epithelial ovarian carcinoma. Primary laparotomy was done in all patients to allow assessment of the abdominal contents and the sites at high risk of surface metastases. Standard primary surgical treatment consisted of hysterectomy, bilateral salpingo-oophorectomy, and infracolic omentectomy. Peritoneal washings and scraping of the diaphragm were not routinely done, except in the Danish patients. Samples were obtained by biopsy or fine-needle aspiration from all suspicious intraperitoneal or retroperitoneal lesions in all patients. Routine paraaortic and pelvic lymphadenectomy was not done, but palpable nodes were sampled.

The tumour capsule was examined for rupture and excrescences (microscopic or macroscopic). The occurrence and timing of tumour rupture was also recorded as preoperative or during surgery. We could not distinguish between intraoperative rupture and that due to surgical needle aspiration; both were classified as rupture during surgery. Dense adhesions were defined as any adherence requiring sharp dissection. Patients with cyst rupture during dissection were not classified as having dense adhesions except when the surgeon reported adhesions requiring sharp dissection. Ascites was defined as in the 1973 FIGO definition[12]—an amount of peritoneal fluid exceeding the normal amount, according to the surgeon, or the presence of malignant cells in the peritoneal fluid. Ascites fluid was examined cytologically in most cases. In this retrospective analysis, we could not estimate the volume of ascites present at surgery. In women with bilateral ovarian tumours, the size of the largest site was recorded. All patients treated before 1988 were originally staged according to the FIGO 1973 classification,[12] in which patients were classified as having ascites when the peritoneal fluid contained malignant cells or when the amount of peritoneal fluid exceeded the normal amount, according to the surgeon. At the time of analysis, they were reclassified retrospectively according to the FIGO 1988 classification.[11] The absence of data on peritoneal cytology and, in some cases, incomplete surgical staging information limited the correct classification according to the FIGO 1988 classification. Patients treated after 1988 were classified according to the new classification, and were also retrospectively grouped according to the 1973 classification.

Policies on adjuvant treatment varied according to time and the country and included no adjuvant therapy, treatment with cisplatin, alkylating agents, or anthracyclines, intraperitoneal phosphorus-32-labelled colloid therapy, abdominopelvic radiotherapy, and pelvic irradiation with or without an alkylating agent. Second-look surgery was not routinely done.

Follow-up examinations took place at the referral hospital or at the local hospital. All patients from Norway, Denmark, and Austria were also followed up with the help of the national cancer registries. These registries were checked in 1993, 1992, and 1995, respectively. The registry staff asked the referring physician or hospital about patients who could not be contacted. The diagnosis of relapse was based on clinical and radiological examinations and was, whenever possible, confirmed by cytology or histology. Treatment of relapse included surgery, radiotherapy, hormonal therapy, and cytotoxic chemotherapy. Various regimens

Characteristic	Number with characteristic (n=1545)	5-year disease-free survival in % (SE)*
Degree of differentiation		
Good	529 (34%)	93·7 (1·1)
Moderate	473 (31%)	81·0 (2·0)
Poor	347 (23%)	60·5 (2·9)
Not graded*	196 (13%)	73·7 (3·6)
FIGO stage (1988)		
Ia	567 (37%)	86·6 (1·5)
Ib	69 (5%)	76·8 (5·5)
Ic	904 (59%)	76·8 (1·5)
Not recorded	5	..
FIGO stage (1973)		
Ia	1022 (66%)	84·0 (1·2)
Ib	141 (9%)	72·0 (4·1)
Ic	377 (24%)	73·3 (2·6)
Not recorded	5	..
Histological type		
Serous	430 (28%)	75·9 (2·2)
Mucinous	410 (27%)	90·8 (1·5)
Endometrioid	354 (23%)	82·2 (2·2)
Clear cell	185 (12%)	72·7 (3·4)
Undifferentiated	49 (3%)	61·5 (7·2)
Mixed epithelial	85 (6%)	76·0 (5·6)
Unclassifiable carcinoma	16	..
Not recorded	16	..
Dense adhesions		
No	667 (43%)	84·5 (1·5)
Yes	346 (23%)	75·7 (2·5)
Not recorded	532 (34%)	78·0 (2·0)
Age (years)		
⩽50	470 (30%)	87·8 (1·7)
>50	1070 (69%)	76·8 (1·5)
Not recorded	5	..
Ascites		
No	1131 (73%)	82·4 (1·2)
Yes	320 (21%)	73·0 (2·8)
Not recorded	94 (6%)	79·4 (5·3)
Extracapsular growth		
No	961 (62%)	83·5 (1·3)
Yes	239 (16%)	72·1 (3·1)
Not recorded	345 (22%)	77·1 (2·6)
Rupture		
No	859 (56%)	83·3 (1·4)
During surgery	122 (8%)	70·2 (4·6)
Before surgery	89 (6%)	71·6 (4·8)
Unknown	475 (31%)	75·4 (5·4)
Size of tumour (cm)†		
<5	23 (1%)	81·3 (8·4)
5–9	198 (13%)	78·3 (3·1)
10–19	533 (35%)	82·5 (1·7)
⩾20	207 (13%)	87·5 (2·4)
Not recorded	584 (38%)	75·7 (2·0)
Country		
Norway	380 (25%)	80·5 (2·1)
Canada	242 (16%)	81·9 (2·5)
Sweden	267 (17%)	81·9 (2·4)
Austria	121 (8%)	80·0 (3·9)
Denmark	277 (18%)	76·2 (2·9)
UK	258 (17%)	80·7 (1·9)

*Clear-cell tumours and mixed epithelial tumours with clear-cell elements were not graded. †For bilateral tumours the largest size is recorded.

Table 1: **5-year disease-free survival in relation to various characteristics of patients**

Characteristic	Hazard ratio (95% CI)	p
Degree of differentiation		
Good *vs* moderate	0·32 (0·21–0·48)	0·0001
Good *vs* poor	0·13 (0·09–0·20)	0·0001
Moderate *vs* poor	0·42 (0·31–0·55)	0·0001
Rupture		
Yes *vs* no	1·46 (1·14–1·87)	0·0027
Before surgery *vs* no	1·89 (1·27–2·80)	0·0013
During surgery *vs* no	1·94 (1·26–2·98)	0·0022
FIGO (1973) stage		
Ia *vs* Ib	0·56 (0·39–0·82)	0·023
Ia *vs* Ic	0·56 (0·43–0·73)	0·0001
Ib *vs* Ic	0·99 (0·66–1·47)	0·94
FIGO (1986) stage		
Ia *vs* Ib	0·54 (0·30–0·96)	0·031
Ia *vs* Ic	0·53 (0·40–0·70)	0·0001
Ib *vs* Ic	0·98 (0·57–1·69)	0·94
Histological type*		
Serous	1·34 (1·04–1·73)	0·023
Mucinous	0·37 (0·25–0·53)	0·0001
Endometrioid	0·88 (0·66–1·18)	0·40
Clear cell	1·68 (1·23–2·30)	0·0012
Undifferentiated	2·54 (1·57–4·10)	0·0001
Mixed epithelial	1·15 (0·68–1·94)	0·60
Age (per year)	1·02 (1·01–1·03)	0·0001
Ascites		
Yes *vs* no	1·67 (1·27–2·18)	0·0002
Size of tumour	0·98 (0·95–1·00)	0·06
Dense adhesions		
Yes *vs* no	1·66 (1·23–2·26)	0·001
Country*		
Norway	0·98 (0·74–1·28)	0·86
Canada	0·89 (0·64–1·23)	0·46
Sweden	0·92 (0·67–1·26)	0·60
Austria	1·01 (0·65–1·58)	0·95
Denmark	1·15 (0·91–1·47)	0·25
UK	0·95 (0·66–1·36)	0·76
Extracapsular growth		
Yes *vs* no	1·85 (1·37–2·50)	0·0001

*Hazard ratio given for each category versus the other categories.

Table 2: **Actuarial disease-free survival related to the most important prognostic factors in stage I ovarian carcinoma by univariate analysis**

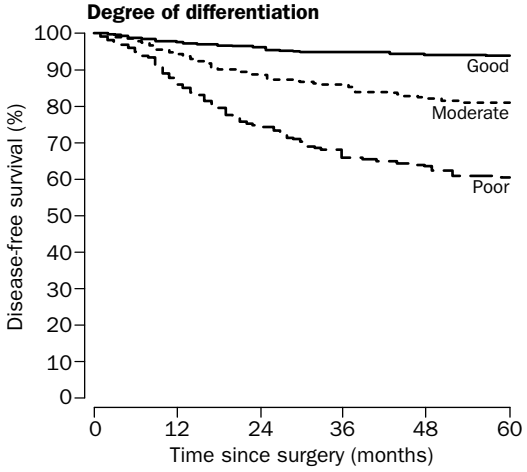
were offered, including cisplatin, carboplatin, alkylating agents, anthracyclines, or new drugs undergoing phase 1 or 2 investigation. Relapses in patients who did not receive adjuvant platin therapy, or who had a treatment-free interval of at least 6 months were mostly treated with cisplatin or carboplatin.

All histological sections were reviewed in the six different centres without knowledge of the clinical outcome. Histological typing used WHO criteria.[13] All tumours were graded according to the degree of architectural differentiation and the cellular features as well, moderately, or poorly differentiated. Clear-cell tumours or mixed epithelial tumours with clear-cell elements were not graded. A tumour was labelled as a clear-cell tumour whenever clear cells were identified.

Analysis

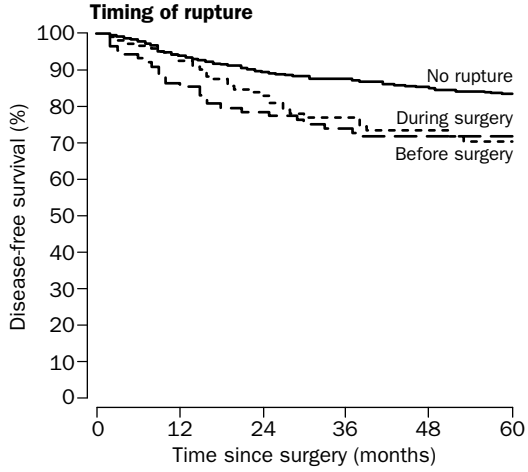
Crude and disease-free survival times were defined as the period between primary surgery and death or relapse, respectively. Patients dying of intercurrent disease were censored at the time of death when the actuarial disease-free survival was calculated. Kaplan-Meier methods and the log-rank test (Mantel-Haenszel) were used to estimate and compare crude and disease-free survival curves. The SAS software package was used for statistical analyses (version 6.12). The independent effects of prognostic factors and other covariates on survival function were determined by Cox's proportional-hazards regression models.

Standard methods require that random censoring be non-informative.[14] Informative censoring can lead to severe biases. We undertook a global sensitivity analysis for informative censoring to test for bias. The idea was to redo the original analyses (univariate and multivariate) under two extreme assumptions about censored cases. One assumption was that an event occurred immediately



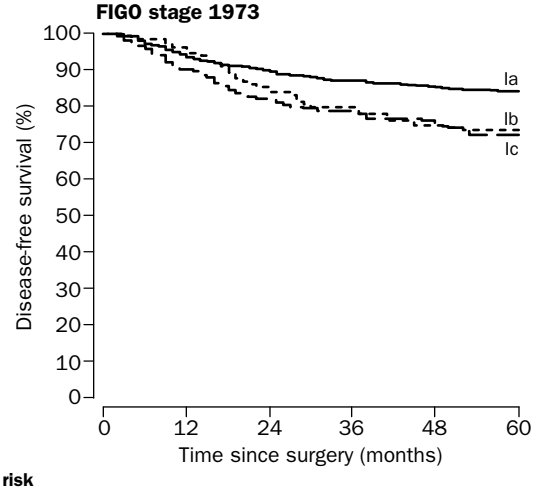
Number at risk

Well differentiated	529	491	469	427	362	302
Moderately differentiated	473	415	364	319	273	216
Poorly differentiated	347	274	223	189	153	122



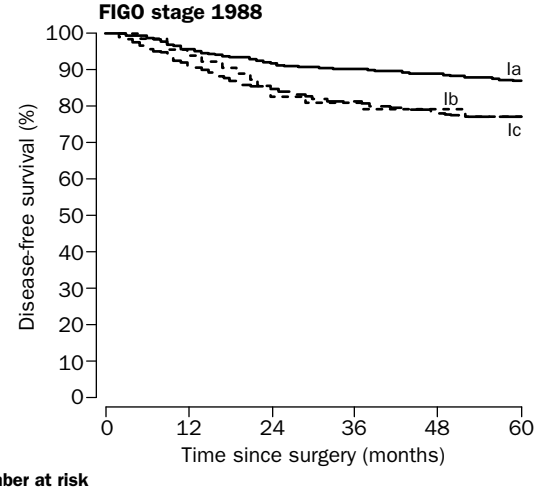
Number at risk

No rupture	859	758	692	618	517	417
During surgery	122	109	89	66	54	35
Before surgery	89	76	69	63	56	51



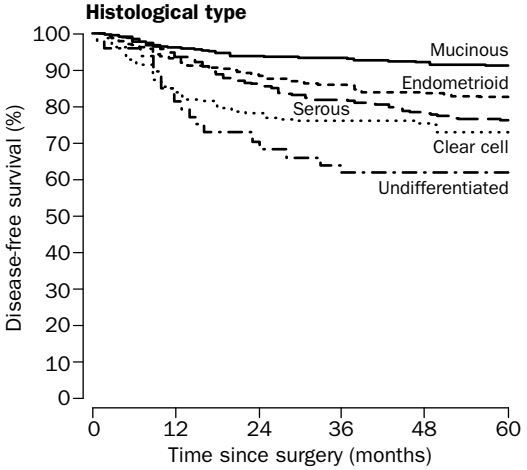
Number at risk

Ia	1022	915	842	764	666	546
Ib	141	124	104	93	73	60
Ic	377	299	257	215	168	137



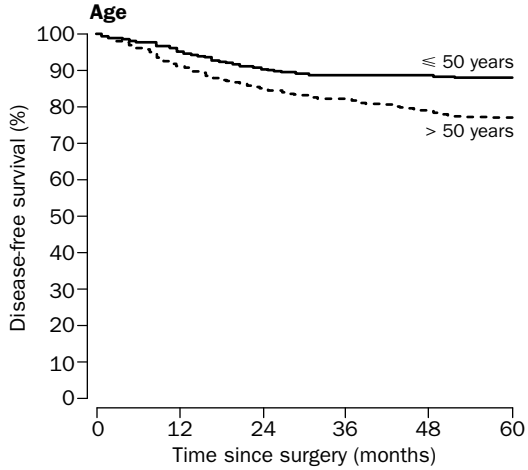
Number at risk

Ia	567	511	474	428	373	302
Ib	69	59	51	48	37	31
Ic	904	766	679	597	497	411



Number at risk

Mucinous	410	366	341	314	273	233
Endometrioid	354	314	286	250	220	185
Serous	430	377	331	295	250	195
Clear-cell	185	150	135	119	98	75
Undifferentiated	49	39	30	27	18	14



Number at risk

⩽ 50 years	470	374	347	322	287	247
> 50 years	1070	789	702	618	513	408

Figure 3: **Actuarial disease-free survival according to prognostic variables**
In the analysis by histology mixed epithelial and unclassifiable carcinomas are not shown.

after censoring. The opposite assumption was that censored cases had a longer time to the event than any one else in the database. Both reanalyses were compared with the original result, and for each covariate the reanalyses bracketed the original estimate. We therefore concluded that in this study observations that were terminated were non-informative.

For the partial likelihood analysis, we did not use Breslow's approximation[15] because the follow-up times were heavily tied.[16] Therefore, we used in the multivariate analysis the exact method.

A stepwise selection procedure (a combination of forward and backward selection) on the proportional-hazards model was used to identify the most important prognostic factors. The analysis was started with the single best prognostic factor on univariate regression analysis. The importance of a prognostic factor was defined in terms of the measure of the significance of the coefficient for the factor (by the Wald statistic) in the Cox model. Candidate variables were accepted only if p was less than 0·2, the significance level of entry (SLE).[17] In a forward step, one by one multivariate Cox proportional-hazards models were made with one of the remaining variables added to the pool of already selected variables for each model. The next candidate variable to enter the pool of selected variables was that with the smallest p value. The candidate was accepted only if p was less than 0·2. When a new variable enters the model, the coefficients of the variables already in the model are affected. Therefore, after every forward step we did a backward step, removing any variable from the model if the significance level had risen above the significance level of staying (SLS) of 0·25. This procedure was iterated until none of the variables outside the model met the SLE criterion when entered in the model and none of the variables in the model violated the SLS criterion.

A best subset selection method was used to validate the results from the stepwise selection procedure. This approach to model building makes use of the branch and bound algorithm of Furnival and Wilson (1974).[18] The selection finds a specific number of models with the highest χ^2 score in a range of model sizes.

Results

With median follow-up of 72 months (range 0–216) in the surviving patients, 345 (22·3%) relapses occurred. The overall actuarial 5-year crude survival (figure 1) was 82·6% (SE 1·0) and disease-free survival was 80·4% (1·0). 5-year disease-free survival was very similar for all countries except Denmark (hazard ratio Denmark *vs* other countries 1·15 [95% CI 0·91–1·47]; figure 2, tables 1 and 2). The frequency distributions of the variables and staging procedures (data available from corresponding author on request) were very similar. Type of surgery and adjuvant therapy did not seem to be significant for disease-free survival (data available on request). Only a few patients were treated conservatively. The types of adjuvant therapy given varied widely, which made further analysis not meaningful. Furthermore, decisions to give adjuvant therapy or use a conservative procedure are based on information available to the treating physician at the time. Hence, these findings are biased and should not be used as prognostic variables.

As in earlier studies,[6,9] disease-free survival was the most sensitive endpoint to establish the prognostic value of the different variables. (Information on crude survival and the relation between different prognostic variables can be obtained from the corresponding author.)

Life-table plots of disease-free survival according to degree of differentiation, rupture, FIGO stage 1973, FIGO stage 1988, histological type, and age are shown in figure 3 and estimated 5-year disease-free survival according to these variables in table 1. The characteristics found to be prognostic factors for disease-free survival in the univariate analyses were degree of differentiation, rupture at any time, rupture before surgery, rupture during surgery, FIGO stage 1973, FIGO stage 1988, histological type, age, ascites, dense adhesions, and extracellular growth (table 2).

All prognostic variables were entered in the multivariate model. Only patients with all variables available were used in the final model. The only factors that were strong and independent predictors of disease-free survival were degree of differentiation, rupture before surgery, rupture during surgery, FIGO stage 1973, and age (table 3). Mucinous histology, endometrioid histology, and ascites remained in the model of nine variables with p values of less than 0·10. In analysis according to the best subset selection method, these nine variables remained in the five best ranking models. The six significant variables remained in all these models.

Characteristic	Hazard ratio (95% CI) on multivariate analysis	p
Degree of differentiation		
Good*	1·00	..
Moderate	3·13 (1·68–5·85)	0·0003
Poor	8·89 (4·96–15·9)	0·0001
Rupture before surgery		
No*	1·00	..
Yes	2·65 (1·53–4·56)	0·0005
Rupture during surgery		
No*	1·00	..
Yes	1·64 (1·07–2·51)	0·022
FIGO stage 1973		
Ia*	1·00	..
Ib	1·70 (1·01–2·85)	0·046
Age (per year	1·02 (1·00–1·03)	0·053

*Reference category.

Table 3: **Significant variables for actuarial disease-free survival in final multivariate model**

Discussion

The main limitation of conclusions derived from previous retrospective studies in stage I ovarian cancer is that most had too few events to allow multivariate analyses to be undertaken with enough confidence. Our study is based on one large database of patients treated in six countries. The similarity between the countries in frequency distribution of the variables and staging procedures justified pooling of the data. Other strengths of this study were review of the histological slides in the six different centres, review of the patients' records with special attention to dense adhesions and occurrence and timing of rupture, and exclusion of all borderline tumours and high FIGO stages.

Ovarian cancer tissue is not homogeneous and histological grade varies with the proportion selected for grading. The lack of reproducibility in grading reflects the lack of well-defined criteria.[19] Our study confirmed, with histological review in six centres, degree of differentiation as the most important independent prognostic factor in stage I ovarian cancer.We therefore strongly advocate the use of the degree of differentiation in clinical decision-making and its inclusion in the FIGO stage I classification.

Cyst rupture before surgery had been suggested as an independent prognostic factor in several studies,[8–10,20] but rupture during surgery was significant only in univariate analyses.[20–22] Our study confirmed that rupture before surgery is an important independent prognostic variable. Despite fears that rupture during surgery may promote metastases and thereby hasten death of the patient, hitherto there has been no convincing evidence that the fear is justified.[23] Our observation that rupture during surgery had an independent unfavourable impact on disease-free survival should stimulate surgeons to avoid rupture during surgery. In this retrospective analysis we could not distinguish between intraoperative spontaneous rupture and rupture due to surgical needle aspiration.

The unfavourable prognostic effect of rupture during surgery was observed in patients who underwent laparotomy; therefore, no firm conclusions can be made for the endoscopic removal of malignant tumours confined to the ovaries. In view of the reports on rapid peritoneal spread after laparoscopic removal of ovarian cancer[24–28] and our findings, laparoscopic removal of ovarian cysts should be restricted to patients with preoperative evidence that the cyst is benign. Should an unexpected malignant lesion be found at laparoscopy and documented by frozen-section histopathological analysis, an immediate staging laparotomy becomes essential.[23–28]

In the study of Dembo and colleagues[2] on stage I disease, degree of differentiation was the most powerful predictor of relapse, followed by dense adhesion and large volume ascites. In our study, dense adhesion was an important prognostic factor in the univariate analysis but was no longer significant in the multivariate analysis. However, Dembo and colleagues defined dense adhesion as those in which sharp dissection was needed, a raw or oozing area was left, cyst rupture resulted from dissection of the adherence, or direct tumour invasion of adjacent structures was observed. In our study, the definition of dense adhesion was stricter (ie, only adhesions for which sharp dissection was needed) and patients with tumour invasion in adjacent structures were, according to the FIGO classification, registered in a higher stage. These differences may explain the conflicting results.

In our study, ascites was not an independent prognostic indicator. However, ascites was defined as in the FIGO (1973) classification (peritoneal effusion that in the opinion of the surgeon was pathological or clearly exceeded normal amounts, or malignant cells on peritoneal cytology). In other studies, the volume of ascites was classified as large if it was more than 250 mL[2] or 100 mL.[7] These amounts seemed to be arbitrarily chosen. In our retrospective study we could not estimate the amount of ascites so precisely. These differences in definitions may have influenced the results.

Peritoneal washings were not done routinely in our study and we had this information in only a small group of patients. Therefore we cannot comment on the prognostic effect. In the 1988 FIGO report,[11] patients treated between 1979 and 1981 were classified retrospectively according to the 1988 classification, although the earlier staging did not require information on cytology of the peritoneal fluid. The same procedure was followed in our study and earlier studies.[2,6,9] With these restrictions, the new classification did not seem to be superior to the 1973 classification.

Extensive surgical staging, including blind biopsy samples of the pelvic peritoneum, the abdominal gutters, the diaphragm, and para-aortic lymph nodes, has been advocated in early ovarian cancer. In our study, the surgical staging procedure was more limited. The extent to which the relapse risk could be explained by occult peritoneal or nodal spread that would have been detected by meticulous surgical staging cannot be assessed. However, survival in the different countries was very similar except for Denmark, where peritoneal cytology and scraping of the diaphragm was mandatory. Furthermore, patients with well-differentiated tumours had 5-year disease-free survival as high as 93·7%. The value of extensive staging, including para-aortal lymphadenectomy can be questioned in patients with well-differentiated tumours.

Various adjuvant treatment modalities (or no adjuvant therapy at all) were used in this study. In many cases adjuvant treatment was chosen on the basis of prognostic factors, so no conclusions can be made on its value. The efficacy of adjuvant treatment can only be established in large prospective randomised trials. Three such studies have been reported, but each was too small to establish the role of adjuvant platin therapy in early ovarian cancer.[4,10,29] The results of two recently closed trials (one by the European Organisation for Research and Treatment of Cancer and one by the UK Medical Research Council), which have randomised, together, more than 900 patients between adjuvant platin therapy or observation, should elucidate the role of adjuvant therapy in stage I ovarian carcinoma.

Several new factors such as tumour-suppressor genes, oncogenes, angiogenesis markers, morphometric variables, proliferation markers, serum CA125 concentrations, and DNA ploidy,[6,10,30] have been suggested as important prognostic variables in stage I ovarian carcinoma. These variables should be examined in large-scale multivariate analyses but could not be analysed in this retrospective study.

Degree of differentiation is the most important independent prognostic factor and should be used in clinical decision-making and in the FIGO classification of stage I ovarian carcinoma. Cyst rupture before or during surgery decreases disease-free survival independently and should be avoided in patients with a possible diagnosis of ovarian carcinoma confined to the ovaries.

Contributors

Ignace Vergote was mainly responsible for the writing of the paper, and was also involved in the development of the new database, the original Norwegian database, and the statistical analysis. Jos De Brabanter, Herman Verrelst, and Joos Vanderwalle were responsible for the statistical analysis. Anthony Fyles was responsible for the Canadian, Kamma Bertelsen the Danish, Nina Einhorn and Kjerstin Sjövall the Swedish, Paul Sevelda the Austrian, Martin Gore the UK, and Janne Kærn and Claes Tropé the Norwegian database. Dirk Timmerman was involved in development of the new database and in the statistical analysis. Marleen Van Gramberen was responsible for the creation of the new database. All investigators were involved in the writing of the paper.

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